500

# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/656,450 | 09/05/2003 | F. Charles Brunicardi | 60710-00002USC1 | 8472 |

7590 03/03/2006

Tamsen Valoir, Ph.D.
Jenkens & Gilchrist
A Professional Corporation
1100 Louisiana, Suite 1800
Houston, TX 77002-5214

| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALENE K | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/656,450 | BRUNICARDI, F. CHARLES | |
| | Examiner | Art Unit | |
| | Magdalene K. Sgagias | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *119-139* is/are pending in the application.

4a) Of the above claim(s) *113-118* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 119-139 are pending.

Claims 113-118 are not entered. Applicants are required to provide a corrected list of all the pending claims in their new application. Appropriate correction is required.

Claims 119-139 are under consideration.

### *Claim Objections*

2. Claims 119, 120, 121, 124, 125, 126, 127, 132 and 136 are objected to because of the following informalities:

Claim 125 and 126 are duplicates of claims 120 and 121. Appropriate correction is required.

Claims 119, 124, 127, 132, and 136 are objected because the phrase "operatively coupled to" is not a recognized art term for a construct composition

### *Specification*

3. The disclosure is objected to because of the following informalities:

In the specification page 1 under prior related applications, Applicant fail to incorporate in line 2 the issued date of the patent number 6716824. Appropriate correction is required.

### *Double Patenting*

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the

examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 119-121, 123-129, 131-134, 136-139 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. U.S. 6,716,824. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims embrace treatment of pancreatic tumor cells in a subject comprising administering to a subject a nucleic acid vector with insulin promoter SEQ ID NO: 1 operatively coupled to a cytotoxic gene wherein the cytotoxic gene in expressed in a pancreatic tumor cell and a prodrug. The breadth of the scope of the claims recited in the instant application is very broad and includes any route of administration of the claimed vector and a prodrug and obviously encompasses the route of direct administration as embraced by the claims 1-3 of U.S. Patent No. U.S. 6,716,824.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119, 124, 127, 132 and 136 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

When the claims are analyzed in light of the specification, instant invention encompasses any cytotoxic gene wherein the cytotoxic gene is expressed in a pancreatic tumor cell in a subject. The specification describes that the present invention is directed to an RIP-tk (rat insulin promoter thymidine kinase) construct that targets pancreatic cells (specification p 7). In analyzing whether the written description requirement is met for the genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification does not provide any disclosure as to what would have been the complete structure of a representative number of cytotoxic genes either within one species or among different species necessary to target pancreatic tumor cells in a subject. While the specification on page 7 lists thymidine kinase as an example, the specification does not provide any disclosure of the structure of any other species of the claimed genus.

Next, then it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, for example other than motif structure, specific features and functional characteristics that would distinguish different members of the claimed genus. In the instant case, the specification fails to describe any identifying characteristics of a cytotoxic gene which will distinguish different species. The specification while listing thymidine kinase as an example of the cytotoxic genes does not provide guidance whether other species of the genus will have any characteristics similar to or different from thymidine kinase.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the cytotoxic gene that will kill a pancreatic tumor cell at the time of the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-139 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating pancreatic adenocarcinoma in a subject comprising directly administering to a subject a nucleic acid comprising a vector with an insulin promoter having SEQ ID NO: 1 operably linked to a cytotoxic gene, wherein the cytotoxic gene is thereby expressed in a pancreatic adenocarcinoma cell wherein administering a prodrug to said subject, wherein the prodrug is converted to a cytotoxic compound by the action of the protein encoded by said cytotoxic gene and thereby killing the pancreatic adenocarcinoma cell wherein the cytotoxic gene is thymidine kinase gene wherein the prodrug is acyclovir, ganciclovir, FIAU or 6-methoxypurine arabinoside, does not reasonably provide enablement for treating a pancreatic tumor in a subject by the way of the claimed method in the instant application. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 119-123 are directed to a method of killing a pancreatic tumor cell in a subject by

administering a nucleic acid vector with an insulin promoter SEQ ID NO: 1 operatively coupled to a cytotoxic gene wherein the cytotoxic gene is expressed in a tumor cell that does not express insulin in combination with a prodrug.

Claims 124-126 are directed to a method of treating pancreatic tumor cells in a subject by administering a nucleic acid vector with an insulin promoter SEQ ID NO: 1 operatively coupled to a cytotoxic gene wherein the cytotoxic gene is expressed in a PDX-1 positive pancreatic tumor cell in combination with a prodrug.

Claims 127-131 are directed to a method of killing a pancreatic tumor cell in a subject by administering a nucleic acid vector with an insulin promoter SEQ ID NO: 1 operatively coupled to a cytotoxic gene wherein the cytotoxic gene is expressed in a pancreatic tumor cell in combination with a prodrug.

Claims 132-135 are directed to a method of killing a tumor cell in a subject by administering an adenoviral vector with an insulin promoter SEQ ID NO: 1 operatively coupled to a cytotoxic gene wherein the cytotoxic gene is expressed in a tumor cell expressing PDX-1 in combination with a prodrug.

Claims 136-139 are directed to a method of killing a PDX-1 expressing tumor cell in a subject by administering a nucleic acid vector with an insulin promoter comprising multiple copies of SEQ ID NO: 2 operatively coupled to multiple copies of SEQ ID NO: 3 or 4 wherein insulin promoter operatively coupled to a cytotoxic gene wherein the cytotoxic gene is expressed in PDX-1 expressing tumor cell in combination with a prodrug.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification

meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

The specification describes that the present invention is directed to selective targeting of pancreatic cells with cytotoxic genes using promoter driven specific cytotoxic genetic constructs and transcription factors, and to methods for using these constructs and transcription factors to treat cancer and other diseases (specification p 7). The specification more specifically further describes that the present invention is directed to an RIP-tk (rat insulin promoter-thymidine kinase) construct that selectively targets insulin secreting cells, such as beta cells and certain human pancreatic ductal carcinoma cells (PDX-1 positive), to cause death (specification p 7).

While the specification provides teachings pertaining to the ability of RIP-tk suicide gene to target PDX-1 positive human pancreatic ductal carcinoma cells (PANC-1 and CAPAN-1 cells) in vitro and in vivo, and further the cell specific cytotoxicity of human pancreatic ductal carcinoma cells can be achieved using a RIP-tk construct and ganciclovir GVC in vitro and as

well as in in vivo transduced pancreatic tumors using an immunodefficient animal mouse model (specification p 12 and examples 2-4, and figure 8), the specification fails to provide any relevant teachings or specific guidance and/or working examples with regard to: (a) killing of a pancreatic tumor cell that does not express insulin in a subject by administering a construct with an insulin promoter having SEQ ID NO:1 operatively linked to a cytotoxic gene and a prodrug; (b) treating a PDX-1 positive pancreatic tumor cell in a subject by administering a construct with an insulin promoter having SEQ ID NO:1 operatively linked to a cytotoxic gene and a prodrug (c) killing a pancreatic tumor cell in a subject by administering a construct with an insulin promoter having SEQ ID NO:1 operatively linked to a cytotoxic gene and a prodrug; (d) killing a PDX-1 positive tumor cell in a subject by administering an adenoviral vector with an insulin promoter having SEQ ID NO:1 operatively linked to a cytotoxic gene and a prodrug; and (e) killing a PDX-1 positive tumor cell in a subject by administering to a subject a vector with an insulin promoter having SEQ ID NO:2 operatively linked to multiple copies of SEQ ID NO: 3 or 4, said insulin promoter operatively linked to a cytotoxic gene and a prodrug. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for killing a pancreatic tumor cell. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims are directed to methods of killing or treating pancreatic tumor cells in a subject by producing a cytotoxic protein in specific pancreatic tumor cells and clearly fall into the realm of gene therapy. The specification has contemplated killing or treating pancreatic tumor cells using the suicide gene thymidine kinase coupled to an insulin promoter such as the rat insulin promoter followed by treating or administering to the individual an effective amount of GVC, acyclovir, FIAU or 6-methoxypurine arabinoside in an amount sufficient to kill or treat

pancreatic tumors (specification p 17-25). The specification also contemplated that the cytotoxic effect may be enhanced by upregulating transcription of RIP-tk, such as for example, addition of factors that upregulate transcription of RIP-tk as for example SEQ ID NO: 3 or 4 (specification p 19). Since the instant specification has failed to provide specific guidance or working examples correlating to killing or treating pancreatic tumor cells in a subject one of skill in the art could not rely on the state of the gene therapy art to treat any pancreatic tumor cell in a subject by way of the claimed methods. This is because the art of gene therapy is an unpredictable art with respect cell targeting, levels of expression of a therapeutic protein necessary to provide therapy, and mode of administration of the therapeutic gene. These issues are discussed by experts in the field of gene therapy while reviewing the state of the art of gene therapy. Verma et al, (Nature, 389: 239-242, 1998) stated that in gene therapy practice considerable problems have been emerged such as the problem of the inability to deliver genes efficiently and to obtain sustained gene expression (p 239). Anderson (Nature, 392: 25-30, 1998) states that there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease (p 25, 1st column) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (p 30). Applicant's claims do recite adenoviral mediated gene delivery of the cytotoxic gene into a tumor cell expressing PDX-1. The specification however, has not provided any specific guidance or teachings with regard to killing a tumor cell in a subject via adenoviral mediated cytotoxic gene expression encompassed by the claims. The specification does not provide guidance and/or working examples for killing a tumor cell in a subject with a tumor cell expressing PDX-1 by administering adenovirus carrying SEQ ID NO: 1 where the transgene is expressed at levels sufficient and a prodrug to kill target tumor cell by systemic administration. At the time of the instant application, Romano, (Stem

Cells, 17: 191-202, 1999) while reviewing the state of the art of adenoviral vectors noted that while adenoviral vectors can infect nondividing cells there is a need for improvement of adenoviral vector design to deal with the problem of immunogenicity (p 197). While progress has been made in recent years for gene transfer in vivo, vector targeting to desired tissues in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Romano et al, (Stem Cells, 18: 19-39, 2000) review the latest development in gene transfer technology and noted that despite the latest significant achievements reported in vector design, it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame (abstract). Romano, (Stem Cells, 17: 191-202, 1999) indicate also that gene delivery systems need to be optimized in order to achieve effective therapeutic interventions (abstract). Numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and the protein function, the fraction of vector taken up by the target population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein produced. While progress has been made in recent years for the in vivo gene transfer, vector targeting in vivo to desired organs continuous to be unpredictable and inefficient. This is supported by numerous teachings in the art. Deonarain (1998, Exp Opin Ther Patents, 8: 53-69, 1998) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long

enough period of time" (p 53, 1st paragraph). Deonarain reviews new techniques under experimentation in the art, which shows promise but states that such techniques are even less efficient than viral gene delivery (p 65, 1st paragraph). Verma reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p 240). In the instant case the specification does not teach as to how to nucleic acid vector having SEQ ID NO: 1, 2, 3 or 4 operatively coupled to cytotoxic gene will be directed to a pancreatic tumor cell in a subject and whether sufficient amount of the cytotoxic gene product could be produced to kill a pancreatic tumor cell in a subject. Furthermore, the specification fails to provide any guidance and/or working examples as to what doses of the claimed nucleic acid vectors will be administered to target a nucleic acid vector to pancreatic tumor cells other than the site of administration. The specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by either systemic administration or direct administration at the site of the pancreatic tumor cell as claimed in the instant application. It should be noted that although as stated above some publication dates of these cited references is prior to the filing date of the instant application, the issues regarding the unpredictability of gene therapy remain the same and have not be resolved by the guidance provided by the instant specification.

With regard to cytotoxic gene and a prodrug mediated gene therapy for killing or treating a pancreatic tumor cells in a subject as contemplated by the instant specification, the state of the art of a cytotoxic gene and a prodrug mediated gene therapy in pancreatic cancer suggests that while some progress has been made to date there are issues that remain, which make the

treatment of pancreatic cancer by cytotoxic gene and a prodrug mediated gene therapy unpredictable. Nasu et al, (Mol Urol, 4(2): 67-71, 2000) noted that viral-mediated transfer of the herpes simplex virus thymidine kinase (HSV-tk) gene has been demonstrated by several investigators to confer sensitivity to nucleoside analogs such as ganciclovir (GCV) in a variety of tumor cells including pancreas, however, it is still in the early stage of its development, with a number of problems to be overcome such as systemic delivery, specific introduction, and specific expression of the target gene are the major issues to be managed in order to establish a relevant treatment (abstract). MacKenzie (Lancet Oncology, 5: 541-49,2004) wile reviewing the state of the art of gene therapy in pancreatic adenocarcinoma noted that suicide-gene therapy has produced variable results in animal studies on pancreatic cancer and while some studies showed that suicide-gene treatment decreased survival of tumor cells in vitro and in vivo however, other studies have not confirmed the efficacy of suicide genes in pancreatic cell lines (p 542, 2nd column under suicide gene therapy). MacKenzie also noted that although suicide gene approach has not been assessed in patients with pancreatic cancer, results from other tumor sites have not been encouraging (p 542, 2nd column under suicide gene therapy). Fogar et al, (EJSO, 29: 721-730, 2003) noted that suicide gene therapy with HSV-tk did not confer GCV sensitivity to pancreatic cancer in vivo and different pancreatic cancer cell lines cause different growth effects and metastasis patterns after inoculation into SCID mice (abstract). Fogar et al, (Cell Mol Biol, 51(1): 61-76, 2005) even three years later while reviewing killer genes in pancreatic cancer therapy and among them the use of suicide genes (HSV-tk and CD for oancreatic cancer gene therapy in vitro and in vivo noted that the lack of a 100% effect for any studied strategy considered alone, indicates the need for combined therapies to achieve a satisfactory treatment of pancreatic tumor (abstract).

In light of the above, it appears that the state of the art is suggesting that cytotoxic gene

and prodrug gene therapy in pancreatic tumor cells might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of cytotoxic gene and prodrug gene therapy in pancreatic tumor cells raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of cytotoxic and prodrug gene therapy in pancreatic tumor cells is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for killing pancreatic tumor cells by cytotoxic gene and prodrug gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject, the lack of direction or guidance provided by the specification for the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject, the absence of working examples that correlate to the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject, the unpredictable state of the art with respect to the cytoxic gene and prodrug gene therapy, and in particular in pancreatic tumor cells, the undeveloped state of the art pertaining to the cytotoxic gene and prodrug killing of a pancreatic tumor cell in a subject, and the breadth of the claims directed to the cytotoxic gene and prodrug killing of a pancreatic tumor cell that does not express insulin or a pancreatic tumor cell that express PDX-1 or any pancreatic tumor cell in a subject, and also the breadth of the claims directed to cytotoxic gene vectors comprising SEQ ID NO: 1 or SEQ ID NO: 2 or SEQ ID NO: 3, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

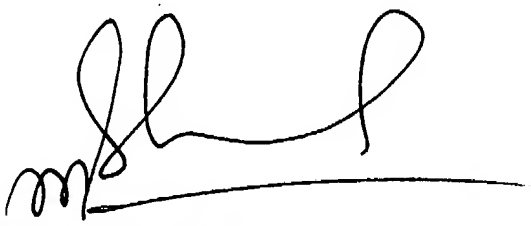
**Conclusion**

**7. No claim is allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Patent Examiner
Art Unit 1632



RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER